CONCEPT PAPER

PREMARKETING RISK ASSESSMENT

DRAFT

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If you plan to submit comments on this concept paper, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include an alternative proposal and the rationale and/or justification for employing the alternative.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*

I. INTRODUCTION

In accordance with Section VIII of the PDUFA III Reauthorization Performance Goals and Procedures, the CDER/CBER Risk Assessment Working Group is drafting a guidance for industry on good risk assessment practices during drug and biological product[1] development. This concept paper is intended to facilitate public discussion on the content of the draft guidance by outlining FDA's proposed approach and requesting comment. Specifically, this concept paper presents FDA's preliminary thoughts on:

- Important risk assessment concepts
- Generation and acquisition of safety data during product development
- Analysis and presentation of safety data in an application for approval

II. IMPORTANT RISK ASSESSMENT CONCEPTS

A. What is risk assessment?

Risk assessment is the process of identifying, estimating, and evaluating the nature and severity of risks associated with a product. Risk assessment occurs throughout a product's lifecycle. To develop a risk management plan and perform pharmacovigilance after approval, it is important to have as good an idea as possible of the product's underlying risks and benefits prior to approval. This process entails ensuring that the body of evidence generated by the clinical trials not only defines the product's effectiveness, but also comprehensively describes its safety (as required by the Food, Drug and Cosmetic Act, which calls for the conduct of all tests reasonably applicable to evaluate a drug's safety).

This concept paper focuses on risk assessment during clinical development, particularly in phase 3 studies. It does not discuss preclinical safety assessments (i.e., animal toxicity testing) or clinical pharmacology programs, because these issues are addressed sufficiently in current FDA and International Conference on Harmonization (ICH)

[1] For ease of reference, this concept paper uses the terms *product* and *drug* to refer to all products (excluding blood products other than plasma derivatives) regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER). Similarly, for ease of reference, this concept paper uses the term *approval* to refer to both drug approval and biologic licensure.

guidances.[2] However, we emphasize that good clinical risk assessment depends on the performance of comprehensive preclinical safety assessments and a rigorous, thoughtful clinical pharmacology program (including elucidation of metabolic pathways, drug-drug interactions, and effects of hepatic and/or renal impairment).

B. Are both premarketing and postmarketing risk assessment addressed in this concept paper?

No, this concept paper focuses solely on risk assessment based on safety data generated during product development. Risk assessment based on data generated from observational data sources (including case reports, case series and pharmacoepidemiologic studies) obtained after a product is marketed is addressed by a separate concept paper entitled *Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.* Programs intended to manage risk could stem from either premarketing or postmarketing risk assessment efforts or both. Such programs are addressed by a third concept paper entitled *Risk Management Programs*.

III. IMPORTANT CONSIDERATIONS IN GENERATING RISK INFORMATION DURING CLINICAL TRIALS

The design of a product's clinical trials program is critical in ensuring that sufficient safety data are generated to allow for approval of the product, as well as to provide data to allow for proper risk management and to inform post-marketing safety assessment. Since many aspects of clinical development have previously been addressed in FDA and ICH guidances,[3] this concept paper presents FDA's thoughts on selected issues as they apply to optimal risk assessment.

A. What is the appropriate size of the premarketing safety database?

The ideal size of a safety database supporting a new product depends on a number of factors, including the novelty of the product, the intended population, the proposed indication (e.g., a treatment for a life threatening disease vs. a symptomatic treatment) and the intended duration of use. In addition, safety concerns identified in the preclinical safety assessment, or safety signals seen in early clinical or human pharmacology studies, could suggest that more intensive safety assessments (including greater patient exposure) would be appropriate.

No guidance currently exists on determining the appropriate size of clinical safety databases for products intended only for acute use or for serious and life-threatening diseases, although 21 CFR part 314 (subpart E) suggests that approval may occur after

[2] FDA and ICH guidances on clinical pharmacology and preclinical programs are available at http://www.fda.gov/cder/guidance/index.htm and http://www.fda.gov/cber/guidelines.htm.

[3] FDA and ICH guidances on clinical development are available at http://www.fda.gov/cder/guidance/index.htm and http://www.fda.gov/cber/guidelines.htm.

phase 2 if benefit is established (i.e., without specific large scale safety studies). On the other hand, most trials designed to show a mortality advantage would be large in the first place and, if successful, would often by themselves demonstrate an acceptable balance of benefit to risk.

FDA would be interested in input on what general guidance could be provided on appropriate sizes of databases for products intended only for acute use and/or for serious and life-threatening conditions. FDA is also interested in input on the proposals below, related to safety assessments of chronically administered drugs for non-life threatening conditions.

For products intended for long-term treatment (e.g., chronic or recurrent intermittent) of non-life-threatening conditions, the ICH has recommended that 1500 patients be exposed to the investigational product.[4] However, the ICH guidance does not specify what patients should be counted towards the 1500 patient target. For chronic use products that are novel in mechanism or class, we believe the 1500 patients should include only those who have been exposed to the product in multiple dose studies of four or more weeks' duration, as many adverse events of concern (e.g., hepatotoxicity, hematologic events) do not usually appear with shorter exposure. Also, ideally, the 1500 patients should have been exposed to doses equal to or exceeding the lowest proposed dose, with a substantial representation of patients exposed at or above the highest proposed doses. In addition, the ICH guidance recommends that 300 to 600 patients be exposed for 6 months or more, with at least 100 being exposed for 12 months.

The ICH E-1 guidance provides a number of considerations that would suggest the need for a larger database, including:

1. When "there is concern that the drug would cause late developing adverse events, or cause adverse events that increase in severity or frequency over time. The concern could arise from:
   - Data from animal studies;
   - Clinical information from other agents with related chemical structures or from a related pharmacologic class;
   - Pharmacokinetic or pharmacodynamic properties known to be associated with such adverse events."

2. When "there is a need to quantitate [sic] the occurrence rate of an expected specific low-frequency adverse event. Examples would include situations where a specific serious adverse event has been identified in similar [products] or where a serious event that could represent an alert event is observed in early clinical trials."

3. When "needed to make risk/benefit decisions in situations where the benefit from the product is either (1) small (e.g., symptomatic improvement in less

[4] *See* Guideline for industry: *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*.

serious medical conditions) or (2) will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations) or (3) is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint)."

4. When "there is concern that a [product] may add to an already significant background rate of morbidity or mortality, and clinical trials need to be designed with a sufficient number of patients to provide adequate statistical power to detect pre-specified increases over the baseline morbidity or mortality."

In addition to the considerations provided in the ICH guidance, other reasons why a larger database could be appropriate include:

1. The proposed treatment is for a healthy population (e.g., chemoprevention, preventive vaccines)

2. A very safe alternative to the investigational product is already available

3. There is the potential for rapid exposure to a large population.

B. What are some characteristics of an ideal safety database?

The composition of an appropriate safety database for a new product would be determined on a case-by-case basis. Ideally, however, all programs would include:

1. Long-term controlled safety studies

Currently, it is common in many clinical programs for much of the patient exposure and almost all of long-term exposure to come from single-arm or uncontrolled studies. In most cases, it would be preferable to have controlled safety data, including long-term safety data, to allow for comparisons of event rates and for accurate attribution of adverse events. Control groups could be given a placebo or an active product, depending on the disease being treated. The usefulness of comparators in longer-term safety studies (versus uncontrolled safety trials) depends on factors such as the background rates of the adverse events of interest. Generally, events that occur rarely and spontaneously (e.g., idiopathic hepatitis) do not need a control group to be interpreted. On the other hand, control groups are essential for detecting changes in rates of events that occur frequently in the population (e.g., death in patients with Alzheimer's). This is particularly true when the adverse event could be considered part of the disease being treated (e.g., asthma exacerbations occurring with inhalation treatments of asthma).

2. A diverse safety database

Ideally, a safety database (and, indeed, the efficacy database) would include a diverse population in phase 3 studies, and only patients with obvious contraindications would be excluded from study entry. Inclusion of diverse populations would allow for the

development of safety data in important demographic groups commonly excluded from clinical trials in the past, such as the elderly (particularly the very old), patients with concomitant diseases, or patients taking common concomitant medications. Broadening inclusion criteria in the studies could enhance the sponsor's ability to generalize findings to the population likely to use the product in the postmarketing period.

3. Development of safety (and effectiveness) data over a range of doses (and plasma levels) throughout the clinical program

These data help to define the exposure-response relationship as it relates to safety and effectiveness. Using a range of doses in phase 3 trials would better characterize the relationship between exposure and the resulting clinical benefit and risk, allowing provision of the best dosing advice. (Labeling for doses in excess of what is needed for effectiveness resulting from inadequate dose exploration increases risk with no potential for gain.) In addition, exposure-response data from clinical trials could provide critical information on the need for dose-adjustments in special populations. Finally, demonstrating a dose-response relationship in late phase clinical trials also could add important information to the assessment of efficacy.

C. How can unanticipated interactions be detected as a part of a safety assessment?

Clinical pharmacology studies do not guarantee a full understanding of all possible risks related to interactions. Ideally, then, risk assessment would address a number of potential interactions either during controlled safety and effectiveness trials or in specific safety trials. This examination for unanticipated interactions should consider the potential for:

1. Drug-drug interactions, particularly with likely concomitant medications (e.g., for a new cholesterol lowering treatment, examining concomitant use of HMG CoA reductase inhibitors and/or binding resins) and/or products known to interfere with the metabolism of the investigational product

2. Product-demographic relationships, by ensuring sufficient diversity of the population (including gender, age, race, genetics)

3. Product-disease interactions by ensuring sufficient variability in disease state and likely concomitant diseases

4. Product-food interactions. This is particularly important when food effects are seen in PK studies and/or metabolism data suggest a likelihood of food effects (e.g., CYP3A4 metabolism, a P-glycoprotein pathway, or when food changes bioavailability)

5. Product-dietary supplement interactions for commonly used supplements that are likely to be co-administered or for which reasonable concerns exist

One important way unexpected relationships can be detected is by incorporating pharmacokinetic assessments (e.g., population PK studies) in clinical trials, including in safety trials. Including PK assessments allows for the determination of exposure-response relationships for both safety and efficacy (e.g., identifying unanticipated new interactions or safety issues or confirming the lack thereof). In addition, such data would allow for better assessment of whether there is a PK contribution underlying any rare, serious, and unanticipated adverse events seen in the clinical trials.

When a product has pertinent safety biomarkers, the markers would be studied during the PK studies and clinical development (e.g., creatine phosphokinase assessments would be used in the evaluation of new HMG CoA reductase inhibitors as a marker for rhabdomyolysis, assessment of QT/QTc effects). If a product has no acceptable safety biomarker, its clinical trials could be used to develop and validate such a marker (though such development would not be generally expected). Although the same dataset would not appropriately be used to both validate and assess the use of the new marker, development and validation of biomarkers during clinical trials could be useful in future trials to address questions regarding product safety.

D. When would comparative safety data be useful?

While comparative safety trials (i.e., trials that incorporate an arm with a well-characterized agent, in addition to the test product) are not generally required in development programs for novel products,[5] such studies could be useful in the following cases:

1. When there is a need to characterize background rates of certain adverse events in order to adequately assess the product

2. When there is a well-established, well-characterized product with minimal toxicity to treat the condition of interest. This examination would be intended to show that the novel therapy has a comparably benign safety profile.

3. When there is a well-established related therapy. This examination could show whether the toxicity profile for the established therapy holds for the novel therapy, or whether important differences exist.

4. When there is a well-established treatment with an effect on survival or irreversible morbidity.

[5] Important exceptions to this general principle exist. For instance, the collection of comparative safety data is standard practice for some products, such as new preventive vaccines.

5. When the sponsor hopes to claim superiority. In this case, it would normally be expected that such comparative superiority claims would be based on more than one controlled study.[6]

E. What are some special considerations for optimal risk assessment during product development?

As mentioned above, good risk assessment practices can vary depending on the product and situation. The following are examples of how risk assessment strategies could be tailored to suit special situations.

1. If a product is chronically-used (and particularly when it has a very long half-life) or has dose-related toxicities, an examination of whether a maintenance dose lower than the initial dose or decreases in dosing frequency from the initial recommended schedule would be appropriate.

2. If a product is to be dose-titrated, data would be developed to define how titration should be performed and what the effects of the titration are on safety (and efficacy).

3. If appropriate, an assessment would be performed of less obvious adverse effects that might not be detected or readily reported by patients (e.g., effects on cognitive function, motor skills, sexual function, mood). These assessments could entail the use of specific psychometric or other validated instruments.

4. If the product is to be studied in pediatric patients, special safety issues would be considered (e.g., growth, neurocognitive development, safety of excipients, universal immunization recommendations and school entry requirements for immunization).

5. In certain circumstances, a large, simple, safety study (LSSS) would be conducted prior to approval. A LSSS is a clinical study designed to assess relatively few outcomes in a large number of patients. These outcomes may be important safety endpoints or other outcomes of clinical importance. Circumstances where an LSSS would be appropriately considered include:

   - When there is a safety signal of concern in the clinical trial database that is not otherwise well answered by the available data or likely to be addressed by remaining outstanding studies (e.g., hepatotoxicity, QT prolongation).

   - When the sponsor is seeking use of the product as a preventative in asymptomatic individuals. The LSSS would be intended to assess the background risk, the effectiveness of the treatment, and the safety of the treatment.

[6] *See* Guidance for industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

- When there are early signals of serious toxicities or other unique or special considerations (e.g., the safety of the use of the product with a concomitant medication). In such cases, the LSSS data could either confirm the magnitude and consequences of any such issues occurring, or show that such concerns are unfounded.

6. A sponsor could consider reserving blood samples (or any other bodily fluids/tissues that may be collected during clinical trials) from some or all patients in phase 3 studies for possible retrospective testing for various biologic assessments, including pharmacogenomic markers, immunogenicity, or other biomarkers. Reserved samples could also allow for retrospective assessment of more routine tests not prospectively conducted. In particular, having samples available for retrospective analysis of pharmacogenomic markers could help to link the occurrence of serious adverse events to particular genetic markers (e.g., haplotypes). However, if a sponsor were to choose to retain samples, appropriate informed consent and ethical considerations would apply.

F. How can sponsors minimize medication errors?

Ideally, a sponsor would conduct a risk assessment to ensure that a product's proprietary name, established name, container label, carton labeling, package insert, and/or packaging do not inadvertently contribute to medication errors. For example, a sponsor could perform a medication error prevention analysis or MEPA to:

1. Identify known and potential medication error modalities
2. Identify potential and actual causes of each error
3. Prioritize the errors according to the expected outcomes
4. Minimize the potential for an error through corrective action including renaming, relabeling or repackaging

Ideally, to assess a product's name, labeling and packaging, a sponsor would:

1. Obtain first-hand information from physicians, pharmacists, nurses, and consumers in inpatient and outpatient settings

2. Use questionnaires, on-duty observations, interviews, simulation testing, computer models, expert panels or focus tests

Although FDA currently undertakes such activities, it would help to minimize medication errors if sponsors also engaged in such risk assessments to support their proposed names, labeling and packaging. Further, having such data from the sponsor could help speed FDA's review of these issues.

G. Are there safety aspects of products that should be addressed in all development programs?

We recommend that the potential for the following serious safety effects be assessed as a part of all new drug development programs:

1. QTc prolongation
2. Liver toxicity
3. Drug-drug interactions
4. Polymorphic metabolism

For new biological products, we recommend that the following serious safety effects be assessed:

1. Therapeutic products - immunogenicity, neutralizing antibodies
2. Biologic products that are live agents – virulence, trasmissibility, genetic stability
3. Transplantation therapies - survival, function, host immunocompetence

IV. IMPORTANT CONSIDERATIONS FOR DATA ANALYSIS AND PRESENTATION

Performing appropriate analyses of safety data acquired from clinical trials is essential to understanding a product's risk profile. Many aspects of data analysis and presentation have been previously addressed in guidance, most notably in FDA's *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* and the ICH guideline for industry *E3 Structure and Content of Clinical Study Reports*. This concept paper does not repeat these guidances, but presents FDA's thoughts on selected issues for public discussion and comment.

A. How can adverse events be described to best ensure that safety signals are identified?

Although it is important to consider investigators' descriptions of adverse events, analysis of the whole safety database requires use of common terminology. In general, sponsors should utilize one coding convention/dictionary throughout a clinical program (e.g., Medical Dictionary for Regulatory Activities or MedDRA). Generally, as an initial approach to data analysis, adverse events can be examined as they were originally coded. However, specific adverse effects or toxicities (particularly those with a constellation of symptoms, signs or laboratory findings) may be reflected by multiple coding terms. When analyzing an adverse event, sponsors should consider the following:

1. By combining related coding terms, it is possible both to amplify weak safety signals, and obscure important toxicities. For example, the constellation of dyspnea, cough, wheezing, and pleuritis might provide a more sensitive, although less specific, appraisal of pulmonary toxicity than any single term. Conversely, combining terms could mask serious, unusual events with more common less serious events (e.g., constipation might include toxic megacolon).

2. It is important to be aware of the possibility that coding methods can divide the same event into many terms. Dividing adverse event terms can decrease the apparent incidence of an adverse event (e.g., including pedal edema, generalized edema, and peripheral edema as separate terms could obscure the overall finding of fluid retention).

Whenever possible, we recommend that the sponsor, in consultation with FDA, prospectively group adverse event terms and develop case definitions. A prospective approach is particularly important for syndromes that are not well characterized by a single term (e.g., serotonin syndrome, Parkinsonism, drug withdrawal). We recognize, however, that some groupings can only be constructed after the safety data are obtained.

B. When do temporal associations between adverse events and product exposure merit analysis?

Analyzing temporal associations between product exposure and adverse events is critical to risk assessment, because it can provide important clues for determining whether the event was product-related.

Time-to-event analyses are appropriate for:

1. Clinically important events that occur on a delayed basis (i.e., events for which even a single occurrence would be important). For example, progression of disability, development of cardiac toxicity, and the need for surgical intervention would be analyzed.

2. Adverse events that occur at initiation of treatment but diminish in frequency over time (e.g., flu-like symptoms with interferons)

Suggested methods for time-to-event analyses include:

1. Descriptions of risk as a function of duration of exposure, or as a function of time since initial exposure, as appropriate (i.e., life table analyses for cumulative incidence)

2. Assessment of risk within discrete time intervals over the observation period (i.e., a hazard rate curve) to illustrate the change in risk over time

3. For events found to be associated with the initiation of treatment that decrease in frequency over time, we suggest supplemental analyses to attempt to discriminate the relative contributions of adaptation tolerance, dose reduction, symptomatic treatment, decreases in reporting, and patient drop out

C. How can analyses of dose effects contribute to risk assessment?

The relationship between adverse events and exposure may help determine whether an event is actually related to the product and, if so, the magnitude of the risk.

Analyses of event rate and severity by dose should be conducted for clinically important adverse events that may be drug-related or that would be expected based on pharmacologic class or pre-clinical data. If there is a range of doses studied, administered dose is the most common way to assess dose-response, but it may be useful to look at rate by weight- or body surface area-adjusted dose, especially if most patients are given the same dose regardless of weight or size. For products administered over prolonged periods, it may be useful to analyze event rates based on cumulative dose. When specific demographic subgroups may be at particular risk of incurring adverse events, exploration of dose-response relationships by demographic subgroup is important. In addition:

1. Although the most reliable information on dose response comes from randomized fixed dose, dose response studies, potentially useful information may emerge from titration studies and from attempts to relate adverse events to plasma concentrations or duration of use.

2. It may also be useful to assess the relation of adverse event rates to the actual doses received preceding the events and to assess adverse events by the cumulative dose at the time of the adverse event.

For products with a stepped dosing algorithm (i.e., incremental dosing based on age or weight), the actual cut points of the paradigm are often arbitrary in nature. It may be useful to make a specific effort to examine safety just above and below the cut points. For example, if the dose of a product is to be 100 mg for patients <80 kg and 150 mg for patients ≥80 kg, an assessment of the comparative safety profiles of patients 75 to 79.9 kg, versus patients 80 to 84.9 kg would be valuable.

D. What is the role of data pooling in risk assessment?

Data pooling refers to the meta-analysis of individual patient data (i.e., retrospectively combining patient-level data from different clinical studies to assess a safety outcome of interest). Used appropriately, pooled analyses can:

1. Allow detection of relatively rare events
2. Enhance the power to detect a statistical association and protect against chance findings in individual studies
3. Provide more reliable estimates of the magnitude and constancy of risk over time

However, a negative result from a pooled analysis does not prove an absence of risk, because the studies may consist of heterogeneous patient populations, and the methods for detecting safety outcomes of interest may not be consistent across the studies. Therefore, data pooling without close attention to the individual studies may diminish the statistical association and the apparent magnitude of the risk.

E. What are appropriate methods for data pooling in risk assessment?

Generally, an appropriately pooled analysis would have the following characteristics:

1. Phase 1 pharmacokinetic and pharmacodynamic studies would be excluded.

2. The risk of the safety outcome of interest would be expressed in person-years, or a time-to-event analysis would be conducted.

3. The patient population in the pooled analysis would be relatively homogeneous with respect to such factors as underlying illness and the studies would have used similar methods of adverse event ascertainment. Alternatively, subgroup analyses would be conducted for patients with different baseline or disease characteristics. Such characteristics could include the disease being treated and disease severity, gender, age, and/or geographic location (particularly US vs. non-US sites).

4. A study-specific incidence rate would be calculated and compared for any signs of case ascertainment differences (recognizing that study to study variation is to be expected).

When the results of a pooled analysis show a diminished statistical association and/or less risk compared to the safety signal originally obtained from one or more of the contributing clinical trials, it could suggest inappropriate use of data pooling. If this occurs, it would be important to ensure that the previously mentioned principles have been appropriately considered in the analysis.

F. What is the role of subgroup analysis in the safety assessment?

Demographic subgroup analyses are required by regulation and other analyses (e.g., effects in people on various background therapies) are also of interest. Subgroup analyses are, like most safety analysis to some degree, almost always exploratory, but can nonetheless be critical in risk assessment. They have the potential to provide a more reliable and relevant estimate of risk for important subgroups of the target patient population.

G. How can the analyses of missing safety data be most informative?

The handling of missing data presents well-known challenges in data interpretation and presentation. Although existing guidances discuss this issue, particularly as it applies to efficacy,[7] ***FDA would be interested in public comment on ways this issue affects risk assessment and/or unique methods that could be used to address the challenge that missing data presents.***

[7] *See* Guidance for industry: *E9 Statistical Principles for Clinical Trials*

H. What are the important aspects of data presentation?

FDA and ICH have provided extensive guidance regarding the presentation of safety data.[8,9] We would supplement these guidances by recommending that certain data be presented for important adverse reactions with emphasis on the following:

1. Relationship of exposure time to the development of the adverse event

2. Summary of adverse event rates using a range of more restrictive to less restrictive definitions (e.g., myocardial infarction versus myocardial ischemia)

3. Summary of the distribution of important demographic variables across the pooled data

4. Where complete case report forms are called for [21 CFR 314.50], there should also be included hospital records, autopsy reports, biopsy reports, and radiological reports, where applicable

5. Assuring that narrative summaries include important supplementary data (e.g., pertinent lab data, ECG data, biopsy data), as previously articulated in guidance.[9]

[8] *See Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.*

[9] *See* Guideline for industry: *E3 Structure and Content of Clinical Study Reports*